37. (New) The method of claim 14, wherein said first and said second sequences are inserted together said first and second sequences each being operably linked to a separate promoter sequence.

38. (New) The method of claim 14, wherein said first and said second sequences are inserted separately said first and second sequences each being operably linked to a separate promoter sequence.

39. (New) The method of claim 11, wherein said first and said second sequences are inserted together said first and second sequences each being operably linked to a separate promoter sequence.

40. (New) The method of claim 11, wherein said first and said second sequences are inserted separately said first and second sequences each being operably linked to a separate promoter sequence.

Please also see a Claims Appendix with a complete listing of the claims as amended without correction marks.

REMARKS

The Office Action of August 14, 2002 has been reviewed and its contents carefully noted. Reconsideration of this case, as amended, is respectfully requested. Applicants thank the Examiner for his thorough and detailed remarks. Claims 1-9, 11-12, and 14-15 are currently pending. Claims 1-4, 7-8, 11, and 14 are amended herein. No claims are canceled herein. New claims 32-40 have been added herein.

Restriction Requirement

In the September 30, 2002 Office Action, though the Examiner announced a Restriction Requirement with regard to the claims and required an election of species under 35 U.S.C. §121. Applicants made a provisional election with traverse at that time relative to the transgenic production of PDGF through microinjection related techniques.

On January 14, 2003, after reviewing the Applicants traverse the Examiner made this Restriction Requirement final. In further response to the Examiner's restriction, Applicants confirm their selection of claims 1-9, 11-12 and 14-15 for continued examination. However, Applicants hereby state that the selection of the pending claims was made without prejudice to Applicants' right to pursue the other method claims or production claims relative to PDGF and its transgenic production in a further divisional application covering the non-elected methods and/or species.

Claim Objections

Applicants thank the Examiner for his comments regarding the informalities present in claims 1, 7-8, 11 and 14. In response the Applicants have amended the claims to more completely address and rectify the Examiner's concerns. Therefore, the prior objections to the clams are rendered moot after having been addressed through specific amendment to each of the relevant claims. The amendments were made to clarify, particularly point out, and distinctly claim the subject matter of the invention. Reconsideration of the objections to the effected claims is respectfully requested.

The Rejections Under 35 U.S.C. §112, first paragraph

Claims 1-22 and 24-32 are rejected under 35 U.S.C. §112, first paragraph for containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make or use the invention. Respectfully, each of the independent claims has been amended to more closely comply with the Examiners suggestions on claim phraseology. With these extensive amendments Applicant asserts that the claims as amended are in condition for allowance and that the rejection is respectfully traversed.

Applicant would like to respectfully point out that in a broad sense the novelty of the patent lies, as expected, in the novel manipulation and engineering of the transgenic mammal and the production and secretion of a physiologically active growth factor in a transgenic animal. That is, the production of PDGF in a living animal has been developed despite the effects that a growth factor may initiate in living tissue. This manner of production is quite distinct from in vitro efforts seen previously, as will be discussed in more detail below. The fact that the prior art did not contemplate the type or degree of genetic manipulation provided for by Applicants, while the Applicants provide and claim a working example and a written protocol of such is the precise reason why the current application is patentable -- it is novel.

The working protocols disclosed in the specification, provide those in the field with the ability to practice the invention, by providing a detailed map leading towards a goal that the Applicant clearly lays out, regardless of the state of the art prior to the application. In conjunction with the extremely high level of skill in the field, it is clear that the specification, as tempered by the relevant caselaw discussed herein and provides more that adequate guidance to make and use the invention. In re Vaeck, 947 F.2d 488, at 496. This along with the Federal Circuit's repeated assertions that in the field of biotechnology the level of skill in the art is necessarily a high one, indicates that the enablement requirements for the instant claims be determined not by the public at large but by scientists already trained in many of the basics of the technology and well-versed in standard protocols. Ajinomoto Co., Inc. v. Archer-Daniels-Midland Co., 228 F.3d 1338, 1340 (Fed. Cir. 2000)("Patents, however, are written to enable those skilled in the art to practice the invention, not the public"); Enzo Biochem v. Calgene, Inc., 188 F.3d 1362 (Fed. Cir.1999).

Given the above amendments and remarks, the Examiners rejection of the claims under 35 U.S.C. § 112, first paragraph, is traversed, and reconsideration of the claims is, respectfully, requested.

New claims 32 through 40 are variously dependent upon independent base claims 1, 8, 11 or 14. Each of these base independent claims has been amended in response to the Examiners concerns. As they retain all the elements of the base claim from which they depend they should be allowable for that reason, as well as for the additional recitations they contain. Applicants therefore respectfully request favorable consideration claims 32-40 under 35 U.S.C. § 112, first paragraph, in view of the above amendments and remarks.

The Rejections Under 35 U.S.C. §103(a)

Claims 1-9, 11-12 and 14-15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Houdebine et al., (U.S. Patent No. 5,965,788 hereinafter the '788 patent), in view of Eichner et al. (U.S. Patent No. 5,665,567 hereinafter the '567 patent), and Hart et al. (Science 240:1529-21, 1988; hereinafter the Hart reference). This rejection of the claims is respectfully traversed.

The basic considerations which apply to obviousness rejections under MPEP § 2141 are as follows:

(1) the claimed invention must be considered as a whole;

(2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(4) reasonable expectation of success is the standard by which obviousness is determined.

When the prior art itself fails to meet even one of the above criteria the cited art does not satisfy 35 U.S.C. § 103(a) and prevents the establishment of the required *prima facie* case of obviousness by the Examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); In re Rijckaert, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). As pointed out below, the prior art not only fails to provide the suggestion, or incentive to combine but also fails to provide any reasonable expectation of success for the piecemeal combination of the prior art into something resembling the instant invention.

Houdebine et al. discloses a conventional method of producing a transgenic animal, but neither claims the production of a Growth Factor such as PDGF, nor offers and specific teaching with regard to this type of molecule in a whole animal setting. Moreover, though the '788 patent and the current claims are tasked to providing a solution to similar problems, the solutions each provides is significantly different, as is reflected in the amended base claims of the current

application. Also of note is the fact (acknowledged by the Examiner in the January 14, 2003 Office Action – page 10) that Houdebine simply fails to teach PDGF specifically either in its production in a transgenic animal or its production in an animal in a physiologically active form. Thus, Houdebine et al. fails to render obvious the instant invention, and therefore independent amended claims 1, 8, 11, and 14 cannot be obvious over Houdebine et al. standing alone.

Eichner et al. does not provide what Houdebine et al. lacks. In the Office Action of January 14, 2003 the Examiner stated that given the Houdebine, Eichner and Hart citations that "the claimed invention as a whole was prima facie obvious" (Office Action of January 14, 2003, page 13, 1st paragraph). However, this ignores the activities of those skilled in the art at the time of this invention, and is contrary to the level of skill present in the art. The Examiner concedes that Houdebine does not disclose and is in fact silent with regard to:

> does not discuss or provide any guidance with regard to the inclusion of any nucleic acid construct in the cells of a host transgenic mammal leading to the expression of a biologically active construct of PDGF; and
>
> fails to mention any teaching with regard to the expression or recovery of any physiologically active PDGF from the milk of transgenic mammals.

Eichner does not make up or these deficiencies. Instead Eichner *et al.*, provides a primer on the production of DNA constructs in an *in vitro* system and the negligible production of a growth factor in mammalian cell *in vitro* conditions. It should also be noted that Eichner is providing for the production of PDGF only in an *in vitro* system and not the vastly more complex milieu of a live animal or specific tissues within that animal. It should be reiterated that the system of the invention is a transgenic living mammal, it is highly unlikely that anyone in the field of transgenics would look to a reference promoting the intracellular production and accumulation of PDGF in in vitro cell culture protocols or procedures for guidance on how to allow or optimize the production of an active PDGF in a whole animal secretory expression system (see Eichner, - Methods). In this light Eichner *et al.*, is simply non-analogous art incapable of supporting an obviousness rejection of the instant claims, or even making itself available for such a combination. There are simply no teachings to allow the methods of Eichner *et al.*, to make themselves available for an artisan in the field of transgenic mammals.

Eichner *et al.*, fails to provide any discussion of any expression system other than *in vitro* cell culture conditions and in this way fails to understand or make obvious the true nature of the instant invention – the systematic use of a wide variety of molecular biology tools to overcome a panoply of expression problems for active PDGF in a transgenic animal system. Given this, the Eichner *et al.* reference is simply inapposite to the invention at hand and fails to provide a disclosure capable of sustaining an obviousness rejection of the instant claims alone or in any combination.

Respectfully, the Examiner must provide more than an odd collection of references that recast known technology. The Examiner must provide references that *knowingly* suggest the combination of protocols, tests, or principles, which will lead to the invention to be rendered obvious, and read upon its claims. The Examiner has not provided these references. Rather the Examiner has suggested that the instant claims are essentially within the purview of ordinary skill. Without more, this is a classic reproduction of the invention from improper hindsight, which cannot be used to negative patentability or establish the required case of *prima facie* obviousness. In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

The important point here is that with regard to the above rejections under 35 U.S.C. §103(a), it should be pointed out that to support the combination of various sources to create an obviousness rejection those sources must themselves specifically contain or objectively suggest to the skilled artisan a combination of art to achieve the invention. To allow anything less would be to render 35 U.S.C. §103(a) a subjective measure of patentability without any parameters or objective standards. This is what the Federal Circuit has squarely decided against in its statements about the improper application of hindsight to sustain an obviousness rejection. This is why the disclosures drawn upon by an Examiner must explicitly contain all the necessary techniques and suggest the combination that would lead to the invention as claimed. In re Dillon, 919 F.2d at 696, 16 USPQ2d at 1904 (Fed. Cir. 1990)(*en banc*); In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Geiger, 815 F.2d 686, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987). This the three cited references do not do. Respectfully, it is thus the objective measure of obviousness that the prior art cited of record is incapable of supporting, thus preventing the maintenance of a 35 U.S.C. §103(a) rejection.

Moreover, the invention of the Appellants required a systematic understanding of the host of problems seen before in the prior art and a novel way of using a variety of complex tools to

produce the raw material for a new class of molecule produced in a novel way. Something which quite simply had not been done before, or reduced to practice. Prior to the elegant solution provided by the Appellants the common practice of those skilled in the art was to attempt production of growth factors in an active form or to attempt expression at extremely low levels.

The Examiner's analysis thus inappropriately bases its rejection on the use of Eichner *et al.*, on the premise that one expression system and all of the interplay in the various tools used to achieve expression of a target protein or protein fragment is like another, and that therefore any cellular expression system with any given target protein is an appropriate and analogous prior art reference for the claimed invention of another such expression system. However, as the Federal Circuit has stated, "[t]wo criteria are relevant in determining whether prior art is analogous: (1) whether the art is from the same field of endeavor, regardless of the problem addressed, and (2) if the art is not within the same field of endeavor, whether it is still reasonably pertinent to a particular problem to be solved," Wang Laboratories, Inc. v. Toshiba Corp. 26 U.S.P.Q. 2d 1767, 1773 (Fed. Cir. 1993); *see also,* In re Clay, 23 U.S.P.Q. 2d 1058, 1060 (Fed. Cir. 1992); (The Wang court found that a prior art reference for using a nine bit controller consisting of nine memory chips encapsulated in ceramic dual in-line packages mounted on a circuit board substrate is not in the same field of endeavor as the claimed nine data memory chips for storing digital data on epoxy glass printed circuit board substrate merely because it relates to memories). Id. The Court further let stand a lower Court finding that the prior art reference was not analogous art and was not reasonably pertinent, i.e. the art would not logically have commended itself to an inventor's attention in considering his problem. Wang at 1773, and Clay at 1061.

The relevance of the Wang analysis to the instant matter lies in the fact that the Eichner reference is not only silent with regard to transgenic animals but rather focuses and provides teaching with regard only to simple expression in eukaryotes – essentially teaching away from the methods required to achieve success in the expression of growth factor sequences in transgenic animals. Respectfully, the concerns for expression of growth factor sequences through various vectors, in prokaryotes or eukaryotes, is an entirely different problem, with an entirely different set of concerns and hurdles preventing success than those inherent in the instant invention. (See Eichner, Discussion, and the Abstract). Thus, though Eichner might contemplate the use of similar sequences as those provided in the instant specification, the problem addressed and the solution provided by Eichner *et al.*, have little or nothing to do with the myriad of expression problems

overcome by the instant claims, therefore falling outside the scope of appropriate art, and making itself unavailable for combination with Houdebine or Hart to render them amended claims obvious.

In a similar situation, the Federal Circuit concluded that as between a method and apparatus in which film is transferred to a welding station and a tape splicing machine capable of handling the same film, "[in] the light of all this evidence, one can reasonably conclude that the reference is not within the field of this inventor's endeavor and was not directly pertinent to a particular problem with which the inventor was involved." King Instrument Corp. v. Otari Corp., 226 U.S.P.Q. 402, 405 (Fed. Cir. 1985); *see also,* Union Carbide Corp. v. American Can Co., 220 U.S.P.Q. 584, 588 (Fed. Cir. 1984).

As in the King and Wang situations, the instant claimed invention is directed to features, methods and solutions of problems which are alien and non-analogous to the prior art cited by the Examiner. Therefore the teachings of Eichner *et al.*, are not pertinent to the claimed invention and cannot render it obvious.

Hart et al. also fails to provide what the Houdebine and Eichner references lack. Hart teaches a the presence of multiple isoforms of the PDGF molecule, but utterly fails to provide a transgenic or whole method of how these isoforms can be effectively expressed, secreted or collected for therapeutic use. Therefore, it does not and cannot make up for the deficiencies found in the prior cited art.

Accordingly, as in *Wang* and *King,* one must conclude that Eichner *et al.* is not within the field of this inventor's endeavor and is not pertinent in any way to the particular problems solved by the invention as provided in the amended claims. Appellants therefore respectfully request the withdrawal of the Rejection of amended claims 1-9, 11-12, and 14-15 under 35 U.S.C. §103(a) as being unpatentable over Houdebine et al., in view of Eichner *et al.* and Hart et al.

New claims 32 through 40 are variously dependent upon independent base claims 1, 8, 11 or 14. Each of these base independent claims has been amended in response to the Examiners concerns. As they retain all the elements of the base claim from which they depend they should be allowable for that reason, as well as for the additional recitations they contain. Applicants therefore respectfully request favorable consideration claims 32-40 under 35 U.S.C. § 103(a), first paragraph, in view of the above amendments and remarks.

Other than a fee for the extension of time no fee is deemed necessary in connection with the filing of this Amendment. However, the Commissioner is authorized to charge any fee which may now or hereafter be due for this application to GTC Biotherapeutics' Deposit Account No. 502092.

Applicants respectfully submit that the pending claims of this application are in condition for allowance, and that this case is now in condition for allowance of all claims therein. Such action is thus respectfully requested. If the Examiner disagrees, or believes for any other reason that direct contact with Applicant's attorney would advance the prosecution of the case to finality, the Examiner is invited to telephone the undersigned at the number given below.

Early and favorable action is earnestly solicited.

Respectfully Submitted,

Date: 7/14/03

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Claim Appendix

1. A method of producing a glycosylated platelet derived growth factor (PDGF) molecule, comprising:

providing a transgenic non-human mammal whose somatic and germ cells comprise a nucleic acid sequence encoding PDGF operably linked to a promoter which directs expression into mammary gland epithelial cells;

obtaining milk from said non-human transgenic mammal, wherein at least 30% of said PDGF in the milk is in a physiologically active dimer form; and,

wherein an insulator sequence is inserted on either side of said nucleic acid sequence encoding PDGF to be transcribed.

2. The method of claim 1, wherein the nucleic acid sequence encodes a PDGF A chain and at least 30% of the dimerized PDGF in the milk is as a PDGF-AA homodimer.

3. The method of claim 1, wherein the nucleic acid sequence encodes a PDGF B chain and at least 30% of the dimerized PDGF in the milk is as a PDGF-BB homodimer.

4. The method of claim 1, wherein the nucleic acid sequence comprises a nucleic acid sequence encoding a PDGF A chain and a nucleic acid sequence encoding a PDGF-B chain wherein at least 30% of said physiologically active PDGF molecule is a heterodimer.

5. The method of claim 4, wherein the nucleic acid sequence encoding the PDGF A chain and the nucleic acid sequence encoding the PDGF B chain are under control of the same promoter.

6. The method of claim 4, wherein the nucleic acid sequence encoding the PDGF A chain is operably linked to a different promoter than the nucleic acid sequence encoding the PDGF B chain.

7. The method of claim 1, wherein the transgenic non-human mammal comprises a nucleic acid sequence encoding a PDGF A chain and a nucleic acid sequence encoding a PDGF B chain.

8. A method of producing a transgenic non-human mammal capable of expressing an active PDGF molecule in its milk, comprising

introducing into a fertilized egg a nucleic acid sequence encoding a PDGF chain operably linked to a promoter which directs expression in mammary epithelial cells;

allowing said fertilized egg to give rise to a transgenic non-human mammal, wherein said transgenic non-human mammal expresses PDGF in its milk and at least 30% of the PDGF is present in the milk is in a physiologically active dimer form;

wherein an insulator sequence is inserted on either side of said nucleic acid sequence encoding PDGF to be transcribed; and,

wherein said physiologically active PDGF molecule is glycosylated.

9. The method of claim 8, wherein the cell is an oocyte.

11. A method of producing a transgenic non-human mammal capable of expressing an active PDGF molecule in its milk, comprising:

introducing into a fertilized egg a first nucleic acid sequence encoding a PDGF A chain operably linked to a promoter which directs expression in mammary epithelial cells;

introducing into said fertilized egg a second nucleic acid sequence encoding a PDGF B chain operably linked to a promoter which directs expression in mammary epithelial cells;

allowing said fertilized egg to give rise to a transgenic non-human mammal, wherein the transgenic mammal expresses PDGF in its milk and at least 30% of the PDGF is present in the milk in a physiologically active dimer form;

wherein said physiologically active PDGF molecule is a heterodimer;

wherein an insulator sequence is inserted on either side of said first and said second nucleic acid sequences encoding PDGF to be transcribed; and,

wherein said physiologically active PDGF molecule is glycosylated.

12. The method of claim 11, wherein the cell is an oocyte.

14. A method of producing a transgenic non-human mammal capable of expressing an active PDGF molecule in its milk, comprising:

providing a fertilized egg from a transgenic non-human mammal whose germ and somatic cells comprise a first nucleic acid sequence encoding a PDGF-A chain operably linked to a promoter which directs expression in mammary epithelial cells;

introducing into said fertilized egg a second nucleic acid sequence encoding a PDGF-B chain operably linked to a promoter which directs expression in mammary epithelial cells;

allowing the cell to give rise to a transgenic non-human mammal, wherein the transgenic mammal expresses PDGF in its milk and at least 30% of the PDGF is present in the milk in active form;

wherein said active PDGF molecule is a heterodimer;

wherein an insulator sequence is inserted on either side of said first and said second nucleic acid sequences encoding PDGF to be transcribed; and,

wherein said active PDGF molecule is glycosylated

15. The method of claim 14, wherein the cell is an oocyte.

32. The method of claim 8, wherein the nucleic acid sequence encodes a PDGF A chain and at least 30% of the dimerized PDGF in the milk is as a PDGF-AA homodimer.

33. The method of claim 8, wherein the nucleic acid sequence encodes a PDGF B chain and at least 30% of the dimerized PDGF in the milk is as a PDGF-BB homodimer.

34. The method of claim 8, wherein the nucleic acid sequence comprises a nucleic acid sequence encoding a PDGF A chain and a nucleic acid sequence encoding a PDGF-B chain wherein at least 30% of said active PDGF molecule is a heterodimer.

35. The method of either claims 1, 8, 11 or 14, wherein said fertilized egg cell is from an ungulate selected from the group consisting of bovine, ovine, porcine, equine, caprine and buffalo.

36. The method of either claims 1, 8, 11 or 14, wherein said promoter sequence is selected from the group consisting of: caseins, β-lactoglobulin, whey acid promoter, and lactalbumin.

37. The method of claim 14, wherein said first and said second sequences are inserted together said first and second sequences each being operably linked to a separate promoter sequence.

38. The method of claim 14, wherein said first and said second sequences are inserted separately said first and second sequences each being operably linked to a separate promoter sequence.

39. The method of claim 11, wherein said first and said second sequences are inserted together said first and second sequences each being operably linked to a separate promoter sequence.

40. The method of claim 11, wherein said first and said second sequences are inserted separately said first and second sequences each being operably linked to a separate promoter sequence.